JACC Vol. 21, No. 4
March 15, 1993:851–5

CLINICAL STUDIES

Immediate Sealing of Arterial Puncture Sites After Cardiac Catheterization and Coronary Angioplasty Using a Biodegradable Collagen Plug: Results of an International Registry

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Objectives. **The aim of this study was to evaluate the safety and efficacy of a biodegradable collagen plug that has been developed to reduce the arterial compression time required to achieve hemostasis at the arterial puncture site after diagnostic and interventional coronary procedures.**

Background. **After diagnostic and interventional coronary catheterization procedures, local arterial compression is required to achieve hemostasis and complications may ensue, especially in patients on full anticoagulation.**

Methods. **Between March 1991 and July 1991, 252 patients admitted for routine coronary angiography or angioplasty to four large hospitals received such a hemostatic device immediately after the procedure. Hemostasis was achieved with collagen in 87% of patients after a mean compression time of 4.8 min. Time to hemostasis was independent of the heparin load. A total of 34 hematomas (21%) was reported; all but 2 resolved without additional treatment. Two patients had a severe hematoma, requiring blood transfusion, and two patients required surgery to repair a pseudoaneurysm. During a follow-up period of 4 weeks no severe late complications were reported.**

Conclusions. **We conclude that the collagen plug appears to be a safe device to achieve hemostasis at the arterial puncture site, independent of anticoagulation.**

(J Am Coll Cardiol 1993;21:851–5)

With the increasing number of diagnostic cardiac catheterizations and therapeutic percutaneous transluminal coronary procedures there is a growing need to limit hospital stay for cost-effective reasons. This has led to an increasing use of smaller caliber arterial sheaths to facilitate performance of such procedures on an outpatient basis. On the other hand, the increasing use of larger caliber new devices, such as atherectomy catheters, stents or circulatory support systems for which intensive use of anticoagulant agents has been advised, is associated with a greater risk of peripheral vascular complications. To shorten compression times required to achieve hemostasis and to reduce arterial complication rates, a biodegradable collagen plug has been developed that enhances the formation of fibrin and the subsequent formation of a clot at the puncture site immediately after a diagnostic or interventional procedure. Purified bovine collagen has been used in surgical procedures since late 1960 as an adjunct to hemostasis when control of bleeding by ligature or other conventional methods is ineffective or impractical.

When collagen comes into contact with blood, platelets aggregate on the collagen and release coagulation factors that, together with plasma factors, result in the formation of fibrin. Anticoagulant prophylaxis by heparin or aspirin does not affect the hemostatic effectiveness of collagen. Once implanted into tissues of an organism, collagen is ultimately degraded and resorbed by granulocytes and macrophages that progressively invade the implant and, through their collagenase system, selectively digest collagen.

In this study we evaluated the safety and efficacy of such a collagen plug in a group of patients admitted for nonemergency cardiac angiography or balloon angioplasty. The primary efficacy measure was defined as the arterial compression time to achieve hemostasis. Also, the incidence of hematoma, hemorrhage and other arterial complications was recorded.

Methods

Patient selection. After experimental animal work in Mount Sinai Medical Center in New York and after initial clinical studies in 20 patients at the St. Antonius Hospital in Nieuwegein, The Netherlands, 252 patients were enrolled between March 1991 and July 1991 at the St. Antonius

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Manuscript received May 20, 1992; revised manuscript received August 12, 1992, accepted September 18, 1992.

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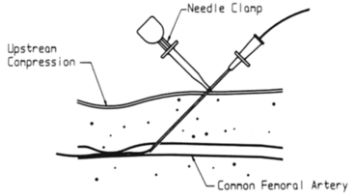


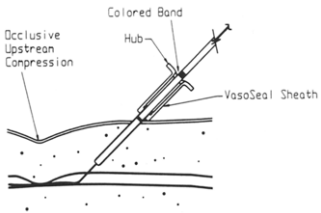
Figure 1. Measurement of the distance between skin and artery at the time of arterial puncture. A needle clamp at the level of the skin indicates the skin-artery distance.

Hospital at Nieuwegein, the Universitäts Klinik at Frankfurt, the Royal Brompton National Heart and Lung Hospital in London and the Mount Sinai Medical Center in New York.

Patients presenting for a routine angiographic study or angioplasty were enrolled after giving informed consent. All patients received the hemostatic device (Vasoseal, Datascope) immediately after the procedure. No effort was made to reverse the effect of anticoagulant agents in any patient. Patients with platelet disorders, a preexistent hematoma, known allergy to beef collagen products or with elevated blood pressure (systolic >220 mm Hg or diastolic >120 mm Hg, or both) uncontrolled by medical therapy were excluded.

Procedure. At the start of the catheterization procedure, the distance between skin and artery was measured by placing a small clamp on the needle where it enters the skin, once the tip of the needle was in the artery (Fig. 1). At the end of the diagnostic or therapeutic procedure, a guide wire was reinserted, the introducing sheath (usually 7F or 8F) removed and a blunt-tipped 11F dilator inserted over the guide wire to a depth corresponding to the skin-artery distance (measured previously) minus 5 mm. An 11.5F applicator sheath was then inserted over the dilator and

Figure 2. Insertion of a skin and subcutaneous tissue dilator at the end of the procedure to provide an entry lumen for the oversized plug. An 11.5F applicator sheath is positioned over this dilator.



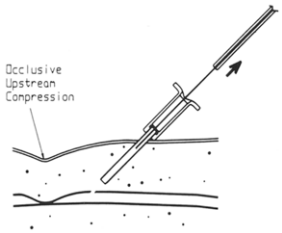


Figure 3. After removal of the wire and dilator, an oversized 11.5F applicator sheath is placed onto the artery so that the plug can be advanced onto the artery. Occlusive upstream arterial compression is applied.

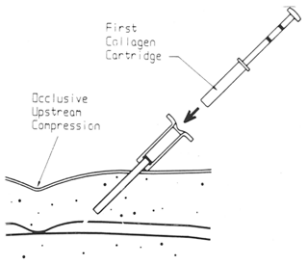
advanced onto the surface of the artery (Fig. 2). After removal of the wire and dilator (Fig. 3), the first plug (100-mg collagen) was applied through the applicator sheath as the applicator sheath was gradually pulled back (Fig. 4). A second plug (100-mg collagen) was then applied (Fig. 5) and the sheath removed (Fig. 6), with some compression maintained for 2 or 3 min. After plug placement, manipulation of the insertion site was avoided.

Statistics. All data are expressed as mean value ± SD. Data were analyzed with the use of the Student *t* test and the Fisher exact test.

Results

Patient data. The 252 patients ranged in age from 22 to 90 years (mean ± SD 58.5 ± 10.9); 200 (79%) were male. Height ranged from 137 to 192 cm (mean 171) and weight from 49 to 114 kg (mean 75.5). One hundred five patients (42%) underwent diagnostic angiography, 129 (51%) underwent percutaneous transluminal coronary angioplasty, 11 (4%) underwent

Figure 4. Application of the first plug (100 mg of collagen) delivered using a cartridge through the applicator sheath.



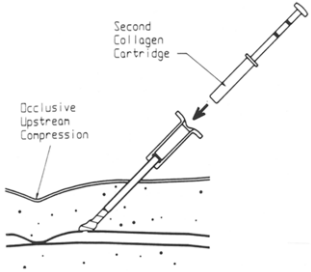


Figure 5. Application of the second plug (100 mg of collagen) through the applicator sheath, filling the space between the first plug and the skin.

coronary angioplasty and intracoronary stent placement, 2 (1%) underwent femoral artery balloon angioplasty and 5 (2%) underwent valvuloplasty.

In the vast majority of cases, arterial access was through the right femoral artery (n = 204 [81%]). Most procedures (n = 212 or [84%]) were conducted with an 8F catheter system. A total of 242 patients (96%) had received aspirin, 198 (79%) were on full heparinization and 71 (28%) were taking oral anticoagulant agents.

The patients undergoing angiography had received a mean of 5,715 ± 4,615 U of heparin compared with 15,378 ± 3,025 U (range 4,000 to 20,000) in the patients undergoing coronary angioplasty. The patients undergoing valvuloplasty had received 10,000 U of heparin. The overall dose of heparin was 11,295 ± 6,032 U. There was no statistically significant difference between the heparin doses for the angioplasty procedures in the participating centers.

Procedural data. Hemostasis was achieved with collagen in 219 (87%) of 252 patients. In 33 (13%) of 252 patients, pressure dressings were required because of an incomplete hemostasis. In two centers pressure dressings were routinely

Figure 6. The applicator sheath is removed after both plugs are placed. Upstream compression of the artery can be stopped.

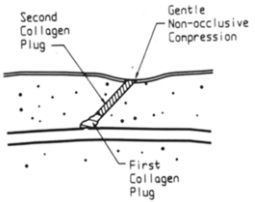


Table 1. Complications Associated With Sealing of the Arterial Puncture Site in 252 Patients

Complications	Patients No.	Patients %
Hematoma		
Mild (<2 cm)	22	9
Moderate (2 to 6 cm)	14	5
Severe (>6 cm)	18	6
Subtotal	54	21
Other events		
Arteriovenous fistula (conservative treatment)	1	0.4
Pseudoaneurysm (with surgical repair)	2	0.8
Aneurysm (small, no surgery)	2	0.8
Bleeding requiring transfusion	2	0.8
Subtotal	7	2.8
Overall events	61	24

used (91 of 99 patients). After angiography, compression times averaged 4.3 ± 2.8 min (range 0.5 to 20). After coronary angioplasty, compression times averaged 5.3 ± 7.6 min (range 0.5 to 45). Overall compression times averaged 4.8 ± 6.0 min (range 0.5 to 45). If average heparin doses and compression times are compared, the time to hemostasis appears to be independent of the heparin load because uniformly short compression times of 4 to 5 min were measured regardless of variation in heparin doses. Moreover, because sheath withdrawal and collagen plug placement occurred immediately after a procedure without heparin reversal, it appears that the device creates hemostasis independent of systemic anticoagulation. Immobilization time ranged from 1 to 24 h (mean 8.3).

Complications. Table 1 provides a summary of complications associated with the procedures conducted in this study. A total of 54 hematomas of various sizes were reported. All but two hematomas resolved without further intervention, and no change in hemoglobin or hematocrit was noted in the 52 patients.

Four events (1.5%) did require additional treatment. Two occurred in patients who experienced a severe hematoma requiring blood transfusions and two in patients who required surgery to repair a pseudoaneurysm that developed 2 days after the procedure. All four patients had an uneventful recovery. One patient developed an arteriovenous fistula that was treated conservatively. The incidence of events appears to be lower in diagnostic angiographic cases than in interventional cases (p = 0.03).

Technical complications including positioning and delivery of the collagen plug onto the arterial puncture site were reported in four patients in this series. All cases involved inability to deliver both plugs at the site because of tearing of the delivery sheath. In two cases hematomas developed that subsequently resolved without further intervention. In the remaining two cases, hemostasis was achieved manually with no resulting complications.

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Table 2. Published Data on Femoral Artery Compression Time After Cardiac Catheterization

Report	Technique	Patients (no.)	Compression Time (min)
Present study	Collagen hemostatic device	252	4 to 8
Eisenberg and Muni (1)	Manual compression	1,900	10 to 15
Semler (2)	A. Manual compression	1,005	33.5
	B. Mechanical compression	2,250	19.2
Lemarbre et al. (3)	Local compression	64	≥20
McMillan and Murie (4)	Local compression	3,500	10
Kern et al. (5)	Compression	287	15

Four-week follow-up findings. In a follow-up period of 4 weeks no severe late complications were reported, and 229 (91%) of 252 patients were followed up for >4 weeks. Renewed puncture of the femoral artery was performed in 14 patients within an interval of 2 days after sealing, usually to perform an angioplasty procedure after earlier cardiac catheterization. Placement of the sheath was difficult in 1 of 14 patients. The majority of patients reported an indolent swelling of the groin that disappeared within 4 to 6 weeks. Two patients reported that transient fever occurred 1 and 2 weeks, respectively, after sealing without evidence of local inflammation, and resolved without therapy within 2 days.

Discussion

Advantages of the collagen hemostatic device. Although concurrent control patients who underwent conventional hemostasis techniques such as manual compression or clamping of the arterial puncture site were not included in this clinical study, data concerning compression times have been published (1–5) and are summarized in Table 2. From our study it is clear that the average 5-min compression time observed with the collagen device is substantially shorter than that obtained with other currently available methods.

Furthermore, the hemostatic properties of the collagen plug are independent of the heparin load. Closure of the puncture site after cardiac interventions constitutes a daily problem for interventional cardiologists because of the time required for compression if the patient has to remain on full anticoagulation, as is advised for patients receiving intracoronary stents (6,7). If the procedure is being carried out with larger introducing sheaths, as is often the case with directional or rotational-ablative atherectomy, the risk of femoral artery complications is further increased if full anticoagulation is also required. It is therefore of major importance that compression times after insertion of a collagen plug to the puncture site not be influenced by systemic anticoagulation.

Incidence and nature of hematoma. A review of published data on the nature of hematoma reveals that such an event is ill defined at best and typically not noted unless surgical repair of the femoral artery is involved. The incidence rate of hematoma requiring surgical intervention is low, typically <1% of cases examined (8–11). Given the lack of criteria for judging hematomas not requiring surgery, it is difficult to judge the 21% incidence rate of hematoma in our series. All hematomas, no matter how minor, have been reported in our study. In contrast, late groin complications such as hematoma were not even included in the 1991 report (12) of the new computerized registry of the Society for Cardiac Angiography and Interventions on 71,916 patients in 1990.

Complications associated with the collagen hemostasis technique. Kern et al. (5) considered a small hematoma to be <5 cm in diameter and reported an incidence rate of 7% in a cohort of 287 patients. If hematomas of 6 cm in our study are used as a basis for comparison, 36 such hematomas (14%) in our study could be classified as small, which may be a higher rate than that reported by Kern et al. (5). However, the incidence rate of severe hematoma (>6 cm in diameter) was only 6% in our study. Although there are no comparable historical published data for comparison, only the two severe hematomas that developed into a pseudoaneurysm required surgical intervention in our study. The incidence of other events is not unexpected for cardiac catheterization procedures. The incidence of arteriovenous fistula, pseudoaneurysm, ischemia or bleeding was <1% (Table 1), a finding compatible with the previously reported rates of <0.5% to 2% (8,13–16). With the exception of the pseudoaneurysm described previously, all of the aforementioned events resolved without major surgical intervention in our study.

Complications after angioplasty. An examination of the distribution of events by procedure indicates that coronary angioplasty procedures accounted for the highest frequency. This is not unexpected, considering the use of larger sheaths and the use of systemic anticoagulant therapy (9,16).

Role of the delivery sheath. Technical complications involving positioning and delivery of the collagen plug as a result of tearing of the delivery sheath were reported in four patients. Initially, positioning of this delivery sheath was made difficult by its one size fits all configuration and the resulting surplus material that interfered with appropriate positioning. Since then, the delivery sheath has become available in a variety of lengths, corresponding to the skin-artery measurements and has been made less pliable. During follow-up study, no complications were reported and no local infections were noted. It seems likely that the low pH (3.0 to 3.2) of the collagen plug reduces the risk of infections.

Risk of collagen insertion. Theoretically, the insertion of collagen into the arterial lumen constitutes the major risk associated with this procedure. The combination of careful measuring of the skin-artery distance, the blunt tip of the dilator and the oversized applicator sheath and collagen plug prevented the occurrence of such an event in this series. In the future, in cases in which even larger catheter systems are used, larger sized plugs and more oversized applicator sheaths should be developed to prevent intraarterial insertion.

In our limited experience to date in closing puncture sites after intraaortic balloon pumping, 11.5F sheaths have been inserted; thus far, we have had no incidence of intraaortic insertion with oversized plugs.

It remains unclear whether mechanical forces play a role in closing the puncture site with this device, in addition to the hemostatic properties.

Conclusions. The collagen plug appears to be a safe device to achieve hemostasis at the arterial puncture site after routine diagnostic angiography or percutaneous transluminal coronary angioplasty. The ability to establish hemostasis with this device independent of anticoagulation may have important implications for interventional procedures in which larger femoral artery sheaths are used in patients under full anticoagulation. However, further clinical experience with the collagen plug is needed before it can be used routinely and safely in the cases in which it would be most needed.

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